REMARKS

Status of the Claims

Claims 169, 171, 172 and 174-198 are in the application.

Claims 188-198 are withdrawn from consideration.

Claims 169, 171, 172 and 174-187 stand rejected.

By way of this amendment, claims 169 and 187 have been amended, claims 188-198 have been canceled, and new claims 199-207 have been added.

Upon entry of this amendment, claims 169, 171, 172, 174-187 and 199-207 will be pending.

Summary of the Amendment

Claim 169 has been amended to more clearly set forth the invention. As amended, claim 169 refers to the "stimulation of accumulation of intracellular cGMP" as the result of activation of guanylyl cyclase C. In addition, the claim has been amended to more clearly set forth the invention as whole by referring the enhanced efficacy of cytotoxic cancer treatment methods resulting from pretreatment with guanylyl cyclase C ligands that activate guanylyl cyclase C sufficient to increase accumulation of intracellular cGMP and inhibit cell proliferation. Support for the amendment is found throughout the claims as field and the specification such as paragraphs [0001], [0072], [0073], [0074], [0077], [0172] and [0173] of the published specification.

Claim 187 has been amended to correct an obvious typographical error.

Claims 188-198, which have been deemed as being directed as a patentably distinct, non-elected invention, have been canceled, and the subject matter is reserved for inclusion in a divisional application.

New claim 199 corresponds to claim 169 as amended except new claim 199 administering the "cytostatically effective amount of a guanylyl cyclase C ligand" "for a period sufficient to inhibit the proliferation of cancer cells". Support for the amendment is found

throughout the claims as field and the specification such as paragraphs [[0138] and [0143] of the published specification.

New claims 200-207 correspond to claims 171, 172, 175, 176, 182 and 185-187 except they are dependent on new claim 199.

No new matter has been added.

Claim Rejections under 35 USC § 103

U.S. Patent No. 5,879,656 in view of Shilubhai et al. in view of Cohen

Claims 169, 171, 172 and 174-187 have been rejected under 35 USC 103(a) as being unpatentable over U.S. Patent No. 5,879,656 in view of Shilubhai et al. (Cancer Res. Sep 15, 2000 60:5151-5157) in view of Cohen (Int Radiat Oncol Biol Phys 1987 13:251-8).

In setting forth its findings, the Office states that U.S. Patent No. 5,879,656 is asserted to teach the following.

> [A]dministering anti-guanylyl cyclase C antibodies, including monoclonal and chimeric, and GCC ligands in conjugated and unconjugated form with therapeutic agents to individuals for therapy of primary or metastasized colorectal cancer.
>
> [T]hat individuals suffering from primary and metastasized colorectal cancer can be readily identified and the compositions of the invention can be used to kill the cancer cells.
>
> [T]hat the pharmaceutical compositions of the present invention may be administered either as individual therapeutic agents or in combination with other therapeutic agents.
>
> [T]hat the treatments of the present invention may be combined with conventional therapies, which may be administered sequentially or simultaneously.
>
> [U]sing intravenous infusion of the compositions and that the dosage is varied depending several factors including pharmacodynamics, route of administration, and kind of concurrent treatment.
>
> [And that] multiple therapeutic agents such as 5-fluorouaracil and bleomycin.

(Official Action, page 3.) In addition, the Office states that

> US Patent No. 5,879,656 teaches that ST/GCC ligands activate the receptor upon binding.

(Official Action, sentence bridging pages 5 and 6.) The Office notes in its findings that US Patent No. 5,879,656

> does not teach the different doses, concentrations, and times of treatment claimed, humanized anti-guanylyl cyclase C monoclonal antibody or treating with calcium.

(Official Action, page 4.)

Shilubhai et al. is asserted to teach that

> uroguanylin inhibits proliferation and induces apoptosis in colon adenocarcinoma cells and suppresses polyp formation.

(Official Action, page 4.)

Cohen is asserted to teach that

> to find the safest procedure for treating a tumor, one must search for that combination of factors which will maximize the conditional probability of controlling the tumor and avoiding injury in any normal tissues, this depends on several factors including dose, field-size, fractions, and time.

(Official Action, page 4.)

Based upon these finding, the Office concludes that

> [i]t would have been *prima* facie obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of USPN 5,879,656 and use different doses and times of infusion of the unconjugated GCC ligands, such as uroguanylin, and antibodies comprising therapeutic agents, because Shilubhai teaches the anti-cancer activity of uroguanylin and Cohen teaches the best tumor treatment scheme is to maximize the chance of tumor control by optimizing factors such as dose and number of fractions and avoid complications. One would have been motivated to use different doses and times of infusion of the GCC ligands in order to optimize the dose needed to effectively treat the colorectal cancer and to avoid complications such as injury to normal tissue. It is noted that optimum suitable ranges may be obtained by routine

> experimentation, absent a showing of criticality or unexpected results.

(Official Action, page 4.) In discussing its conclusion, the Office notes that

> optimum suitable ranges may be obtained by routine experimentation, absent a showing of criticality or unexpected results. Additionally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller,* 220 F.2d 454, 456, 105 USPQ 233,235 (CCPA 1955). See MPEP 2144.05(11).

(Official Action, page 4.)

Claim 169 has been amended to more clearly set forth the invention as a whole, thereby highlighting the features which more clearly distinguish the claimed invention from the prior art. The claims recite methods of treating individuals who have "metastasized colorectal cancer or primary or metastasized gastric or esophageal cancer" by administering to such individuals who have been

> identified as having metastasized colorectal cancer or primary or metastasized gastric or esophageal cancer

a combination of compounds administered in sequential steps. As set forth in the claims, first

> a cytostatically effective amount of a guanylyl cyclase C ligand sufficient to inhibit cell proliferation by the cytostatic effect of the guanylyl cyclase C ligand for at least 6 hours wherein, wherein said guanylyl cycles C ligand activates guanylyl cyclase C on cancer cells, and stimulates accumulation of intracellular cGMP

is administered to the individual. Reference to the stimulation of the "accumulation of intracellular cGMP" was added by amendment to further clarify the activity and effect on cells by the "cytostatically effective amount of a guanylyl cyclase C ligand sufficient to inhibit cell proliferation". The claims recite that

> subsequently after administration of said guanylyl cycles C ligand is completed administering a therapeutically effective amount of a cytotoxic therapeutic agent or radiation.

As amended, the claims expressly states that the

> effectiveness of said therapeutically effective amount of a cytotoxic therapeutic agent or radiation is enhanced by prior inhibition of proliferation of cancer cells by said cytostatically effective amount of said guanylyl cyclase C ligand.

Applicant urge that nothing in the combination of references discloses that activation of GCC renders cells more susceptible to radiation or cytotoxic agents. As disclosed in the specification, GCC activation leads to elevated levels of cGMP which inhibit and slow the cell's progress through the cell cycle. Administering radiation or cytotoxic chemotherapy after activation of GCC has been completed renders the cells more sensitive to radiotherapy or cytotoxic chemotherapy. Nothing in the combined teachings in the art teaches or suggests the invention as claimed.

Nothing in U.S. Patent No. 5,879,656 nor Shilubhai, or Cohen, alone or in combination disclose or suggest that GCC activation renders cells more vulnerable to radiotherapy or cytotoxic chemotherapy administered after GCC activation. Nothing in the combination of references teaches or suggests that pretreatment with a GCC activating compound will result in a more effective use of cytotoxic chemotherapy or radiation therapy by reducing the therapeutic index of the cytotoxic chemotherapy or radiation therapy as set forth in the specification.

As amended, the claims include reference to the features which clearly distinguish the claimed invention over the cited art, i.e., that activation of GCC renders cells more susceptible/vulnerable to radiation or cytotoxic agents, and that pretreatment with a GCC activating compound will result in a more effective use of cytotoxic chemotherapy or radiation therapy by reducing the therapeutic index of the cytotoxic chemotherapy or radiation. As amended, the features which distinguish the claimed invention as a whole form the cited are expressly set forth in the claims.

As amended, the subject matter of claims 169, 171, 172 and 174-187 is not obvious in view of and it therefore patentable over U.S. Patent No. 5,879,656 in view of Shilubhai et al. in view of Cohen. Applicants respectfully request that the rejection the claims 169, 171, 172 and 174-187under 35 USC 103(a) as being unpatentable over U.S. Patent No. 5,879,656 in view of Shilubhai et al. in further view of Cohen be withdrawn.

U.S. Patent No. 6,767,704 in view of Shilubhai et al. in view of Cohen

Claims 169, 171, 172, 174-187 have been rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6,767,704 in view of Shilubhai et al. (Cancer Research, Sep. 15, 2000 60:5151-5157), and in further view of Cohen (Int J Radiat. Oncol. Biol. Phys, 1987, 13:251-8).

In setting forth its findings, the Office states that U.S. Patent No. 6,767,704 is asserted to teach the following.

> [A]dministering conjugated and unconjugated GCC ligands and anti-guanylyl cyclase C humanized monoclonal antibodies with therapeutics to individuals for therapy of primary or metastasized colorectal, stomach or esophageal cancer
>
> [T]hat the compositions of the invention can be used to kill the cancer cells.
>
> [T]hat the pharmaceutical compositions of the present invention may be administered either as individual therapeutic agents or in combination with other therapeutic agents.
>
> [T]hat the treatments of the present invention may be combined with conventional therapies, which may be administered sequentially or simultaneously.
>
> [U]sing intravenous infusion of the compositions and that the dosage is varied depending several factors including pharmacodynamics, route of administration, and kind of concurrent treatment.
>
> [And that] multiple therapeutic agents such as 5-fluorouaracil and bleomycin.

(Official Action, page 7.) In addition, the Office states that

> given that US Patent No. 6,767,704 teaches administration of the antibodies and conventional chemotherapies, such as the described therapeutic agents, in combination sequentially or simultaneously, one of skill in the art would immediately envision administering the antibody and different therapeutic agents in the claimed order.

(Official Action, page 7.) The Office also notes that US Patent No. 6,767,704

> does not teach the different doses, concentrations, and times of treatment claimed, or treating with calcium.

(Official Action, page 7.)

Shilubhai et al. is discussed above. The Office further notes that Shilubhai et al. that "GCC ligands activate guanylyl cyclase C upon binding." (Official Action, pages 9.)

Cohen is discussed above.

Based upon these finding, the Office concludes that

> [i]t would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of USPN 6,767,704 use different doses and times of infusion of the unconjugated GCC ligands, such as uroguanylin, and antibodies comprising therapeutic agents, because Shilubhai teaches the anti-cancer activity of uroguanylin and Cohen teaches the best tumor treatment scheme is to maximize the chance of tumor control by optimizing factors such as dose and number of fractions and avoid complications. One would have been motivated to use different doses and times of infusion of the GCC ligands in order to optimize the dose needed to effectively treat the colorectal cancer and to avoid complications such as injury to normal tissue. It is noted that optimum suitable ranges may be obtained by routine experimentation, absent a showing of criticality or unexpected results.

(Official Action, page 7.) In discussing its conclusion, the Office notes that

> optimum suitable ranges may be obtained by routine experimentation, absent a showing of criticality or unexpected results. Additionally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the

> optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP 2144.05(11).

(Official Action, paragraph bridging pages 7 and 8.)

Claim 169 has been amended to more clearly set forth the invention as a whole, thereby highlighting the features which more clearly distinguish the claimed invention from the prior art. The claims recite methods of treating individuals who have "metastasized colorectal cancer or primary or metastasized gastric or esophageal cancer" by administering to such individuals who have been

> identified as having metastasized colorectal cancer or primary or metastasized gastric or esophageal cancer

a combination of compounds administered in sequential steps. As set forth in the claims, first

> a cytostatically effective amount of a guanylyl cyclase C ligand sufficient to inhibit cell proliferation by the cytostatic effect of the guanylyl cyclase C ligand for at least 6 hours wherein, wherein said guanylyl cycles C ligand activates guanylyl cyclase C on cancer cells, and stimulates accumulation of intracellular cGMP

is administered to the individual. Reference to the stimulation of the "accumulation of intracellular cGMP" was added by amendment to further clarify the activity and effect on cells by the "cytostatically effective amount of a guanylyl cyclase C ligand sufficient to inhibit cell proliferation". The claims recite that

> subsequently after administration of said guanylyl cycles C ligand is completed administering a therapeutically effective amount of a cytotoxic therapeutic agent or radiation.

As amended, the claims expressly states that the

> effectiveness of said therapeutically effective amount of a cytotoxic therapeutic agent or radiation is enhanced by prior inhibition of proliferation of cancer cells by said cytostatically effective amount of said guanylyl cyclase C ligand.

Applicant urge that nothing in the combination of references discloses that activation of GCC renders cells more susceptible to radiation or cytotoxic agents. As disclosed in the

specification, GCC activation leads to elevated levels of cGMP which inhibit and slow the cell's progress through the cell cycle. Administering radiation or cytotoxic chemotherapy after activation of GCC has been completed renders the cells more sensitive to radiotherapy or cytotoxic chemotherapy. Nothing in the combined teachings in the art teaches or suggests the invention as claimed.

Nothing in U.S. Patent No. 6,767,704 nor Shilubhai, or Cohen, alone or in combination disclose or suggest that GCC activation renders cells more vulnerable to radiotherapy or cytotoxic chemotherapy administered after GCC activation. Nothing in the combination of references teaches or suggests that pretreatment with a GCC activating compound will result in a more effective use of cytotoxic chemotherapy or radiation therapy by reducing the therapeutic index of the cytotoxic chemotherapy or radiation therapy as set forth in the specification.

As amended, the claims include reference to the features which clearly distinguish the claimed invention over the cited art, i.e., that activation of GCC renders cells more susceptible/vulnerable to radiation or cytotoxic agents, and that pretreatment with a GCC activating compound will result in a more effective use of cytotoxic chemotherapy or radiation therapy by reducing the therapeutic index of the cytotoxic chemotherapy or radiation. As amended, the features which distinguish the claimed invention as a whole form the cited are expressly set forth in the claims.

As amended, the subject matter of claims 169, 171, 172 and 174-187 is not obvious in view of and it therefore patentable over U.S. Patent No. 6,767,704 in view of Shilubhai et al. in view of Cohen. Applicants respectfully request that the rejection the claims 169, 171, 172 and 174-187 under 35 USC 103(a) as being unpatentable over U.S. Patent No. 6,767,704 in view of Shilubhai et al. in further view of Cohen be withdrawn.

Claim Objections

Claim 187 has been objected to because a duplicate comma is present on the fourth line of claim 187. Claim 187 has been amended to correct this obvious typographical error and the

grounds for objection to claim 187 have been obviated. Withdrawal of the objection to claim 187 is respectfully requested.

Double Patenting

Non-statutory Obviousness-type Double Patenting

Seven different rejections of claims 169, 171, 172, 174-187 are included in the Official Actin based upon the ground of nonstatutory obviousness-type double patenting. They are as follows:

Claims 169, 171, 172, 174-187 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-58 of U.S. Patent No. 5,879,656 in view of Shilubhai et al. and in view of Cohen.

Claims 169,171, 172, 174-187 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10-13 of U.S. Patent No. 5,962,220 in view of U.S. Patent No. 5,879,656, in view of Shilubhai et al. 60:5151-5157, previously cited), and in view of Cohen.

Claims 169, 171, 172, 174-187 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 6-8 of U.S. Patent No. 6,060,037, in view of U.S. Patent No. 5,879,656, in view of Shilubhai et al., and in view of Cohen (.

Claims 169, 171, 172, 174-187 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 14-17 of U.S. Patent No. 6,087,109 in view of U.S. Patent No. 5,879,656, in view of Shilubhai et al., and in view of Cohen.

Claims 169, 171, 172, 174-187 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-46 of U.S. Patent No. 7,744,870 in view of U.S. Patent No. 5,879,656 in view of Shilubhai et al. and in view of Cohen.

Claims 169, 171, 172, 174-187 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-46 of U.S. Patent No. 7,854,933 in view of U.S. Patent No. 5,879,656 in view of Shilubhai et al and in view of Cohen.

Claims 169, 171, 172, 174-187 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 21 of co-pending application 11/494,901, in view of U.S. Patent No. 5,879,656 (Waldman March, 1999), in view of Shilubhai et al. (Cancer Research, Sep. 15, 2000 60:5151-5157, previously cited), and in view of Cohen (Int J Radiat. Oncol. Biol. Phys, 1987, 13:251-8, previously cited).

In each instance the cited claims of the base reference are asserted to claim compositions or methods related to the use of compounds comprising a ST receptor binding moiety; and an active moiety. In each instance, the base claims recited in the double patenting rejection do not specifically teach administering an additional cytotoxic therapeutic agent or radiation. U.S. Patent No. 5,879,656, Shilubhai et al. and Cohen are discussed above.

In each case, the Office concludes that

> It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use additionally cytotoxic therapeutic agents like 5-FU and bleomycin

Applicants urge that in each instance, the combination of the cited claims and references do not discloses that activation of GCC renders cells more susceptible to radiation or cytotoxic agents. As disclosed in the instant specification, GCC activation leads to elevated levels of cGMP which inhibit and slow the cell's progress through the cell cycle. Administering radiation or cytotoxic chemotherapy after activation of GCC has been completed renders the cells more sensitive to radiotherapy or cytotoxic chemotherapy. Nothing in the combined teachings of the cited claims and references teach or suggest the invention as claimed.

In each instance, nothing in cited claims and references, alone or in combination disclose or suggest that GCC activation renders cells more vulnerable to radiotherapy or cytotoxic chemotherapy administered after GCC activation. In each instance, nothing in the cited claims and references teaches or suggests that pretreatment with a GCC activating compound will result in a more effective use of cytotoxic chemotherapy or radiation therapy by reducing the therapeutic index of the cytotoxic chemotherapy or radiation therapy as set forth in the specification.

As amended, the claims include reference to the features which clearly distinguish the claimed invention over the cited claims and references, i.e., that activation of GCC renders cells more susceptible/vulnerable to radiation or cytotoxic agents, and that pretreatment with a GCC activating compound will result in a more effective use of cytotoxic chemotherapy or radiation therapy by reducing the therapeutic index of the cytotoxic chemotherapy or radiation. As amended, the features which distinguish the claimed invention as a whole form the cited are expressly set forth in the claims.

Applicants respectfully request that the rejection of claims 169, 171, 172, 174-187 on the ground of nonstatutory obviousness-type double patenting as set forth above be withdrawn.

Provisional Non-statutory Obviousness-type Double Patenting

Claims 169, 171, 172, 174-187 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 21 of co-pending application 11/494,901, in view of U.S. Patent No. 5,879,656, in view of Shilubhai et al. and in view of Cohen.

Applicants urge that the reasons set forth above for each of the rejections on the ground of nonstatutory obviousness-type double patenting apply to the provisionally rejection of claims 169, 171, 172, 174-187 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 21 of co-pending application 11/494,901, in view of U.S. Patent No. 5,879,656, in view of Shilubhai et al. and in view of Cohen. Applicants request withdrawal of the rejection in view of the reasons set forth above. Moreover, the rejection is provisional.

Conclusion

Claims 169, 171, 172, 174-187 and 199-207 are in condition for allowance. A notice of allowance is earnestly solicited. Applicants invite the Examiner to contact the undersigned at 610.640.7855 to clarify any unresolved issues raised by this response.

The Commissioner is hereby authorized to charge any deficiencies of fees and credit of any overpayments to Deposit Account No. 50-0436.

Respectfully submitted,

/Mark DeLuca, Reg. No. 33,229/
Mark DeLuca
Registration No. 33,229

Dated: December 22, 2011
PEPPER HAMILTON, LLP
400 Berwyn Park
899 Cassatt Road
Berwyn, PA 19312-1183
Telephone: 610-640-7855
Facsimile: 610-640-7835